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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/434,345	11/05/1999	TENI BOULIKAS		3841

7590 05/08/2002

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EXAMINER
NGUYEN, DAVE TRONG

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/434,345	Applicant(s) BOULIKAS, TENI	
	Examiner Dave Nguyen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Claims 1, 5, 11, 12, 13, 16-18, 22, 23 have been amended, claim 29 has been added by the response filed Feb. 15, 2002.

Claims 24-28 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) MPEP 821.01.

Elected claims 1-23, and 29 are pending for examination.

The specification is objected under Sequence Rules 1.821 because the specification does not conform to the requirements of 37 CFR 1.821 because the specification contain DNA sequences (p. 23-26, for example) for which there is no indicated SEQ ID NO:__ identifier for the DNA sequences. The requirement for compliance in 37 CFR 1.821(c) is directed to "*disclosures* of nucleotide and/or amino acid sequences." (Emphasis added.) All sequence information, whether claimed or not, that meets the length thresholds in 37 CFR 1.821(a) is subject to the rules. Sequence rules 37 CFR 1.821(d) requires the use of SEQ ID No: even if the sequence is embedded in the text of the description or in the claims. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims. The requirements of 37 CFR 1.821 through 1.825 for the reason(s) is set forth on the attached Notice to Comply With The Sequence Rules. A complete response to this office action must have a response to the requirements of 37 CFR 1.821 through 1.825.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 16-23 are rejected under 35 USC 102(e) as being anticipated by either Needham (US Pat No. 5,882,679) or Abra *et al.* (US Pat No 6,126,966)

The claims embrace a product by process, namely an encapsulated cisplatin obtainable by the method of claims 11 or 13, and conventional tumor treatment method of administering intravenously the encapsulated cisplatin.

Needham teaches the same on columns 4, 5, 11-12, 18 (lines 35-67) 38, and 39. Abra *et al.* Teach the same throughout the patent disclosure (column 4, column 13 or 14).

Absent evidence to the contrary, the encapsulated cisplatin produced by the method of Needham or Abra is the same that of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 7-21, 23 and 28 are rejected under 35 USC 103(a) as being unpatentable over Abra *et al.* (US Pat No. 6,126,966) taken with Needham (US Pat No. 5,882,679) and Shaw (US Pat No. 6001817).

Abra *et al.* teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a vesicle-forming lipid, *e.g.,* DSPE (distearyl phosphatidyl glycerol) derivatized with a hydrophilic polymer (PEG which has been derivatized via a linking agent which is itself negatively charged, see Figure 3) and/or cholesterol, and/or HSPC is effective for use to increase the stability of cisplatin during its *in vivo* delivery via intravenous route to a tumor site (claim 1, columns 5 through 6, columns 9-12, column 14). Column 2, third paragraph, specifically discloses that cisplatin is entrapped in the liposomes at a drug-to-lipid ratio of between about 10 to 20 ug/mg total lipid. Column 9, 7th paragraph discloses that 50-200 mg/ml of total lipids (MW: 2748 for DSPE-PEG 2000 or 2772 for DSPG-PEG -2000) is mixed with 8.5 mg/cisplatin (MW: 300) containing buffered solution. In addition, column 9 bridging column 10 discloses the step of mixing a lipid/cisplatin mixture with at least 30% ethanol solution to form encapsulated cisplatin. Abra *et al.* Do not teach incorporations of micelles contained in the liposomes so as to increase the stability of the encapsulated cisplatin/liposomes and the retention of cisplatin, wherein the micelles are associated with cisplatin by ionic interactions).

However, at the time the invention was made, Needham provides a solution to the problem of insolubility of cisplatin that affects that activity of cisplatin and the integrity of the liposomal bilayes (column 4 bridging column 5, column 38, lines 38-67, by mainly incorporating a micellar structure coupled with polymers (PEG which is hydrogen acceptor) and/or cholesterol (column 22) within any conventional liposomal structure including phosphatidyl glycerol (column 8, line 52) so as to increase the solubility and retention of active agents or molecules that are insoluble (column11 through column 12). Column 12, second and third paragraphs, and column 12 bridging column 13,specifically teach that ionic micelles can be formulated by active agents with charges opposite to that designed into the micelles. Column 18 discloses that active agent containing micelles can be routinely made by the prior art and that the micelles can be suspended in a buffer such as water or saline solution. Claim 12 of column 39 clearly embraces cisplatin as

one of the active agents which is associated with micelles contained in a liposomal carrier .

In addition Shaw teaches that buffered solution containing additional excipients including at least 30% ethanol is used to reconstitute cisplatin in a pharmaceutical composition.

It would have been obvious for one of ordinary skill in the art to have incorporated micellar structure coupled with polymers and cholesterol within the liposomal structure so as to increase the solubility and retention of active agents or molecules that are insoluble (column 11 through column 12), wherein the micellar structure is associated to cisplatin by ionic interactions. One would have been motivated to do so because Needham provides a solution to the problem of insolubility of cisplatin that affects that activity of cisplatin and the integrity of the liposomal bilayers by mainly incorporating a micellar structure coupled with polymers and/or cholesterol within the liposomal structure so as to increase the solubility, retention, and activity of active agents or molecules that are insoluble.

It would also have been obvious for one of ordinary skill in the art to have employed the step of reconstituting cisplatin in at least a 30% ethanol solution. One would have been motivated to do so because Abra on column 9 bridging column 10 discloses the step of mixing a lipid/cisplatin mixture with an ethanol solution to form encapsulated cisplatin, and/or because Shaw teaches that buffered solution containing additional excipients including at least 30% ethanol is used to reconstitute cisplatin in a pharmaceutical composition.

It would also have been obvious for one of ordinary skill in the art to have further employed a suitable lipid, *e.g.,* cholesterol, DSPE and/or HSPC, and a hydrophilic polymer as stabilizer complexes to enhance the stability of the liposome taught by the combined cited references. One of ordinary skill in the art would have been motivated to have employed the stabilizer complexes in the liposomes of the combined cited references because both Abra *et al.* and Needham teach that a liposomal composition containing an entrapped cisplatin compound which is composed of a vesicle-forming lipid derivatized with a hydrophilic polymer (PEG), and/or cholesterol, and/or HSPC is effective for use to increase the stability of cisplatin during its *in vivo* delivery to a tumor site (claim 1, columns 5 through 6, columns 9-12).

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 9, 13, 16, 17 and 19-21 are rejected under 35 USC 103(a) as being unpatentable over Abra *et al.* (US Pat No. 6,126,966) taken with Needham and Shaw, and further in view of Unger *et al.* (US Pat No. 6,028,066).

The combined cited references of Abra *et al.*, Needham and Shaw teach the encapsulation method of claim 9 as indicated above.

To the extent that the combined cited references do not teach explicitly the use of hyaluronic acid - DSPE in the method, it would have been obvious for one of ordinary skilled in the art to have incorporated any glycosaminoglycan including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references, particularly glycosaminoglycan is routinely employed in the prior art to increase the stabilization and antithrombic properties of the lipid complexes. One of ordinary skill in the art would have been motivated to have employed including hyaluronic acid in any of the lipid stabilizer complex taught by the combined cited references because of the reasons set forth in the immediately preceding sentence and because Unger *et al.* teach that lipid complexed with hyaluronic acid can be used a stabilizer in any liposomal delivery composition (column 23, last paragraph).

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 1, 2 and 5 are rejected under 35 USC 103(a) as being unpatentable over Abra *et al.* (US Pat No. 6,126,966) taken with Needham and Shaw, and further in view of Lee *et al.* (US Pat No. 5,908,777).

The combined cited references of Abra *et al.*, Needham and Shaw teach the encapsulation method of claims 1 and 2 as indicated above.

To the extent that the combined cited references do not teach explicitly the use of a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution entrapped in the liposomal composition, Lee *et al.* teach that a lipidic complex containing a fusogenic peptide enhances the fusion and delivery of the lipid complex

through cell membrane of a target cell (column 7 citing Haensler and Szoka), and that fusogenic peptide can be derivatized by adding a string of negatively-charged amino acids (glutamic acid residues) at the N or C-terminus of the peptide so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution (column 7).

It would have been obvious for one of ordinary skill in the art to have further employed a fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution. One of ordinary skill in the art would have been motivated incorporate a fusogenic peptide fusogenic peptide derivatized with a string of 1-6 negatively-charged amino acids at the N or C-terminus as a ionic complex with the cisplatin/lipid micelles of the combined cited references because Lee *et al.* teach that a lipidic complex containing a fusogenic peptide enhances the fusion and delivery of the lipid complex through cell membrane of a target cell (column 7 citing Haensler and Szoka), and that fusogenic peptide can be derivatized by adding a string of negatively-charged amino acids (glutamic acid residues) at the N or C-terminus of the peptide so as to enable the electrostatic binding to positively charged cisplatin/lipid complex in an aqueous solution.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

Claims 1, 2, 5 and 6 are rejected under 35 USC 103(a) as being unpatentable over Abra *et al.*, Needham and Shaw, and further in view of Lee *et al.* (US Pat No. 5,908,777) and Gebeyehu *et al.* (US Pat No. 5,334,761).

The rejection of claims 1, 2 and 5 as being unpatentable over Abra *et al.*, Needham and Shaw, and further in view of Lee *et al.* is applied here as indicated above. To the extent that the combined cited references do not teach the use of a cationic lipid/DOPE complex as an additional fusogenic substance so as to enhance the transport of the cisplatin/lipid complex of the combined cited references, Gebeyehu *et al.* is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioactive compounds across the cell membrane of a target cell

(entire document, abstract, column 1, column 4).

It would have been obvious for one of ordinary skill in the art to have further employed any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex as taught by combined cited references. One of ordinary skill in the art would have been motivated to have added any suitable cationic lipid/DOPE complex in the combined cisplatin/lipid/fusogenic peptide complex because Gebeyehu *et al.* is one of many exemplified references that teach that cationic lipid/DOPE complex due to its enhanced affinity to cell membrane are routinely employed in the prior art to enhance the delivery of bioactive compounds across the cell membrane of a target cell (entire document, abstract, column 1, column 4), and because one would have expected that the addition of a fusogenic cationic lipid/DOPE complex would further generate an additive fusogenic effect so as to enhance the delivery of the cisplatin compound to target tumor cells.

Thus, the claimed invention as a whole was *prima facie* obvious over the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Base claims 1, 5, and claims dependent there from are indefinite because it is not apparent as to which of the three components: buffer, lipid, and cisplatin, is referred by the molar ratio of 1: 1 or 1: 2. A change to "wherein the molar ratio between cisplatin and the lipid derivative is 1:1 to 1:2" is suggested (also see page 32 for the written support for the suggested phrase).

Applicant's response filed Feb. 15, 2002 to the previous grounds of rejection is moot in view of the new grounds of rejection as set forth in this stated rejection.

No claim is allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER

Application No.: 09/434,345

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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